



Local anesthetics: review of pharmacologic aspects and clinical properties

(This *Clinical Update* is part one of a three-part series.)

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Purpose

Local anesthetics are the most frequently utilized drugs in dentistry (1). It is essential for clinicians to be aware of the pharmacologic properties of these agents in order to effectively control pain and safeguard the patient. The purpose of this clinical update is to review the pharmacologic aspects and clinical properties of the local anesthetics currently used in dentistry.

The following topics will be reviewed in forthcoming *Clinical Updates* as we continue our series on local anesthetics:

Part II: Assessment of adverse reactions and drug interactions

Part III: Use in medically complex patients

Pharmacotherapeutics

All local anesthetics currently used in dentistry share a fundamental configuration with the first true local anesthetic, cocaine (2). In 1905 the first synthetic solution, procaine (Novocain®), was introduced and served as the standard local anesthetic until the introduction of lidocaine in 1952 (3). Lidocaine transformed the practice of dentistry and today remains the gold standard against which all new local anesthetics are compared.

Properties of an ideal anesthetic:

- Potent
- Reversible
- Rapid onset and adequate duration of action
- Minimal adverse reactions
- Sufficient tissue penetration
- Inexpensive, stable in solution, and sterilizable

Components of a local anesthetic:

- Anesthetic agent
- Vehicle
- Buffers
- Antioxidants
- Vasoconstrictor

The vehicle in local anesthetics is sterile water with sodium chloride, which maintains the osmotic balance between the anesthetic solution and body tissues. Buffers include sodium hydroxide and hydrochloric acid, which are used to adjust the pH and reduce the oxidation of vasoconstrictors. The antioxidant most frequently used in anesthetics is sodium metabisulfite, which is added to prevent the oxidation of the vasoconstrictor (4). Methylparaben was previously used as a preservative in anesthetic carpules but due to its high potential for allergic reactions, it was removed from single dose cartridges and currently is found only in multidose anesthetic vials (1,4). The addition of vasoconstrictor and sodium metabisulfite lowers local anesthetic solution pH, resulting in a slower onset of action and an increased "burning" sensation during injection (4).

Classification and structure

Local anesthetics are classified chemically as amides and esters. These agents are weak bases, tertiary amines with three structures in common:

- **aromatic group** - confers lipid solubility and allows nerve membrane penetration;
- **intermediate chain** - differentiates anesthetic as ester or amide;
- **amino group** - contributes water solubility which prevents precipitation of anesthetic.

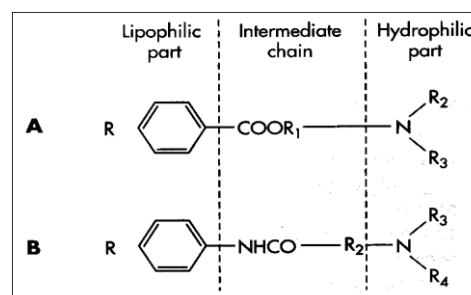


Figure 1. Typical local anesthetic. A: Ester type B: Amide type
Reprinted from Handbook of local anesthesia, 4th ed. SF Malamed, 1997 with permission from Elsevier Science (4).

Ester anesthetics are metabolized more quickly and are considered less toxic than amides. However, the rapid breakdown of esters results in a short duration of action. Ester anesthetics are also more likely to cause allergic reaction than amides. The increased risk of toxicity associated with amide anesthetics is counteracted by their longer duration of action, quicker onset, higher potency, more profound depth of anesthesia, and very low allergenic potential (4,5).

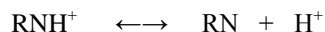
In the United States all commercially available local anesthetics are amides. These are lidocaine (Xylocaine®, Octacaine®, Alphacaine®), mepivacaine (Carbocaine®, Isocaine®, Arestocaine®), prilocaine (Citanest®), bupivacaine (Marcaine®), etidocaine (Duranest®), and articaine (Septanest®, Ultracaine®, Septocaine®). Articaine, which has been used in Europe and Canada for a number of years, received FDA approval for use in the United States in April 2000 (6). Procaine (Novocain®), the last ester anesthetic available for clinical use, was removed from the U.S. market in January 1996 (4).

Mechanism of action

The site of action of local anesthetics is believed to be the nerve membrane. In nerve cells, action potentials are created by the influx of sodium ions from the surrounding tissues (2). These action potentials result in the conduction of nerve impulses that produce sensations, including pain. Local anesthetics prevent the conduction of impulses by decreasing the permeability of nerve membranes to sodium ions (2,3). By impeding the influx of sodium ions into the neuron, local anesthetics block the conduction of impulses, prevent excitation along a neural pathway, and give rise to anesthesia.

Pharmacodynamics and pharmacokinetics

In their natural form, local anesthetics are weak bases, unstable in air, poorly soluble in water, and of little clinical value. In order to be made clinically useful, they are acidified with hydrochloric acid to form salts, which are stable and hydrophilic (3,4). The salt within the solution exists simultaneously in two forms: uncharged base molecule (RN) and positively charged molecule (RNH⁺) (1).



The ratio of base (RN) to cation (RNH⁺) is determined by tissue pH and pK_a (dissociation constant) of the anesthetic (3,4). The ratio of cation to base can be calculated using the Henderson-Hasselbach equation:

$$\log_{10} \text{base/acid} = \text{pH} - \text{pK}_a$$

The lower the pK_a value of the anesthetic, the more basic the solution becomes. More basic solutions have a quicker onset of action than less basic ones (2,3,4). Table 1 illustrates the onset of action as it relates to the pK_a of the anesthetic:

| Table 1. Onset of action as related to anesthetic dissociation constant (pK _a) (3) | | | |
|--|-----------------|-------------------------|-----------------------------------|
| Agent | pK _a | %base (RN) at pH of 7.4 | Approximate onset of action (min) |
| Mepivacaine | 7.7 | 33 | 2 to 4 |
| Articaine | 7.8 | 29 | 2 to 4 |
| Lidocaine | 7.8 | 29 | 2 to 4 |
| Etidocaine | 7.9 | 25 | 2 to 4 |
| Prilocaine | 7.9 | 25 | 2 to 4 |
| Bupivacaine | 8.1 | 17 | 5 to 8 |
| Procaine | 9.1 | 2 | 14 to 18 |

Factors that increase the acidity of the environment can delay the onset of action. Such factors include tissue infection, inflammation, and the inclusion of vasoconstrictors and preservatives. In addition, inflammatory exudates enhance nerve conduction. In the presence of infection or inflammation, it is therefore recommended to use the anesthetic with the lowest pK_a (the most basic solution) and without vasoconstrictors (e.g., mepivacaine).

Duration of action is increased by:

- stronger binding properties of the anesthetic to membrane proteins
- decreased tissue vascularity
- addition of vasoconstrictors

Duration of action is classified as short (30 minutes of pulpal anesthesia), intermediate (60 minutes of pulpal anesthesia), and long (over 90 minutes of pulpal anesthesia). The duration of pulpal anesthesia is generally one-fifth to one-fourth the length of soft tissue anesthesia. Short duration anesthetics include plain formulations of lidocaine, prilocaine, and mepivacaine. Intermediate duration anesthetics are lidocaine, articaine, mepivacaine and prilocaine with epinephrine. Long duration anesthetics are bupivacaine and etidocaine (3,4).

Dosages

Dosages are affected by the patient's age, weight, liver and kidney function, and the type of anesthetic used. The following dosages are recommended for healthy adults:

| Table 2. Maximum adult doses of local anesthetics (4) | | |
|---|------------------------|--------------------|
| Drug | Max. adult dosage (mg) | Max. # of carpules |
| Lidocaine 2% 1:100,000 epinephrine 1:50,000 epinephrine | 500 (300) | 08 11 05 |
| Mepivacaine 2% | 400 (300) | 08 |
| Mepivacaine 3% 1:20,000 levonordefrin | 400 (300) | 05 11 |
| Bupivacaine 0.5% 1:200,000 epinephrine | 90 | 10 10 |
| Etidocaine 1.5% | 500 | 15 |

Dosages are for healthy adults. Values in parentheses are more conservative recommendations. Higher values are manufacturer's recommended dosages. All cartridges contain 1.8 ml of solution except for articaine, which contains 1.7 ml of solution (3,4).

Metabolism and Excretion

Amide anesthetics are metabolized by liver enzymes and excreted by the kidneys. Individuals with compromised blood flow to the liver (alcoholics, liver disease, CHF) and renal disease will have lowered toxicity thresholds. Dosages and frequency of injection may need to be adjusted accordingly (2,3,7).

Vasoconstrictors

Local anesthetics are frequently compounded with sympathomimetics which act as "chemical tourniquets." Vasoconstrictors that are currently used in commercially available local anesthetic preparations in the U.S. include epinephrine (1:100,000, 1:50,000, and 1:200,000) and levonordefrin (1:20,000). Levonordefrin has one-fifth the potency of epinephrine, and therefore is formulated in a higher concentration (4). Vasoconstrictors reduce the systemic absorption of local anesthetics, resulting in increased depth and duration of anesthesia, enhanced local hemostasis, reduced systemic toxicity and an increased margin of safety. Conversely, vasoconstrictors can delay wound healing due to transient tissue ischemia, cause post-operative bleeding after rebound vasodilation, increase the acidity of anesthetic solutions, and, most significantly, cause systemic alterations in cardiovascular patients and other susceptible individuals which may require dosage restrictions (2,4).

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